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Palladium-Catalyzed Asymmetric Arylation of 4,7-Dihydro-1,3-dioxepin. Catalytic Asymmetric Synthesis of γ-Butyrolactone Derivatives

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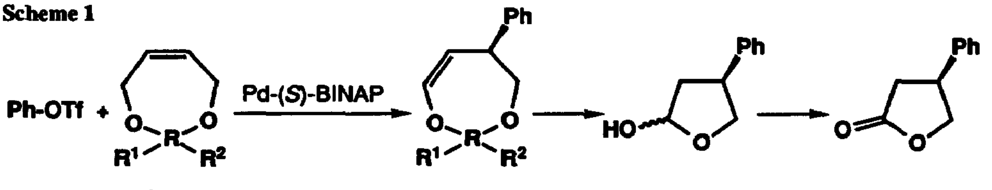
Abstract: *The palladium-catalyzed asymmetric arylation of 4,7-dihydro-1,3-dioxepin* ***1d*** *has been shown to give* ***2d-h*** *(up to 75% ee), which can be readily converted to γ-butyrolactone derivatives. The important role of molecular sieves in the asymmetric Heck reaction has been also clarified.*

We recently reported the first example of an asymmetric Heck reaction,[1] and since then, we[2] and others[3] have demonstrated that this C-C bond-forming reaction is quite useful for the preparation of various optically active compounds. In an effort to extend the scope of this reaction, we examined its potential in the synthesis of 5-aryl-4,5-dihydro-1,3-dioxepin derivatives,[4] which were expected to be readily converted to β-aryl-γ-butyrolactones. In this report, we present a catalytic asymmetric synthesis of 5-aryl-4,5-dihydro-1,3-dioxepins **2d-h** (up to 75% ee) and β-phenyl-γ-butyrolactone **4** (72% ee) from 4,7-dihydro-1,3-dioxepin **1d**, and discuss the important role of molecular sieves in the asymmetric Heck reaction.

Scheme 1



1a-d **2a-d** **3** **4**

a: R=C, R^1=R^2=CH_3 **c**: R=Si, R^1=R^2=*tert*-Bu
b: R=C, R^1,R^2=$(CH_2)_5$ **d**: R=C, R^1=R^2=H

Initial work focused on the direct, one step synthesis of optically active lactol **3** from *cis*-2-butene-1,4-diol and phenyl triflate.[5] However, the asymmetric Heck reaction of these substrates was extremely slow; treatment of phenyl triflate with 4 equiv of *cis*-2-butene-1,4-diol in the presence of $Pd(OAc)_2$ (3 mol %), (*S*)-BINAP[6] (9 mol %), and *N,N*-diisopropylethylamine (3 mol eq) in benzene at 50 °C gave lactol **3** in only 24% yield after 12 days. Moreover, the enantiomeric excess of **3** was only 36%, as determined by HPLC analysis (DAICEL CHIRALPAK AS, hexane-2-propanol, 4:1) of butyrolactone **4** (**3** → **4**; Ag_2CO_3 on celite, toluene, 80 °C). Suspecting that these results were caused by the low solubility of *cis*-2-butene-1,4-

diol in benzene[7] and the instability of the resulting lactol 3,[8] we decided to study the asymmetric Heck reaction of protected *cis*-2-butene-1,4-diol derivatives, specially of 4,7-dihydro-1,3-dioxepin **1d** and its analogs **1a**, **1b**, and **1c** in terms of their synthetic utility.[4,9]

The palladium-catalyzed asymmetric arylation of 4,7-dihydro-1,3-dioxepin derivative **1a** was studied first. Unfortunately this substrate was found to afford the desired coupling product **2a** in only 16% ee and 5% chemical yield even under the best conditions (BINAP in benzene). Surprisingly, however, the addition of 3A molecular sieves[10] to the reaction medium accelerated the asymmetric Heck reaction, improving not only the chemical yield (44%) but also the enantiomeric excess (47% ee). To further improve both the enantiomeric excess and yield, prochiral substrates **1b**, **1c**, and **1d** were also subjected to similar reaction conditions, and the results are summarized in Table 1. It is noteworthy that exposure of **1d** (4 equiv) to $Pd(OAc)_2$ (3 mol %), (*S*)-BINAP (9 mol %), phenyl triflate, and K_2CO_3 (1.5 mol eq) in benzene at 60 °C for

Table 1. Palladium-Catalyzed Asymmetric Arylation of 1a-d.[a)]

entry	1	R	R^1	R^2	molecular sieves	time (d)	yield (%)[d)]	ee (%)
1	**1a**	C	CH_3	CH_3	none	3	5	16[e)]
2	**1a**	C	CH_3	CH_3	MS3A	5	44	47[e)]
3	**1b**	C	$(CH_2)_5$		MS3A	8	49	5[e)]
4	**1c**	Si	*tert*-Bu	*tert*-Bu	MS3A	10	13	37[e)]
5[b)]	**1d**	C	H	H	MS3A	3	82	67[f)]
6[b,c)]	**1d**	C	H	H	MS3A	3	84	72[f)]

a) All reactions were carried out in benzene at 65 °C using 1 (4 equiv), $Pd(OAc)_2$ (3 mol %), (*S*)-BINAP (9 mol %), and K_2CO_3 (3 mol eq) unless otherwise noted. b) K_2CO_3 (1.5 mol eq) was used. c) The reaction was carried out at 60 °C. d) Isolated yield. e) Determined by HPLC analysis of 4. f) Determined by HPLC analysis.

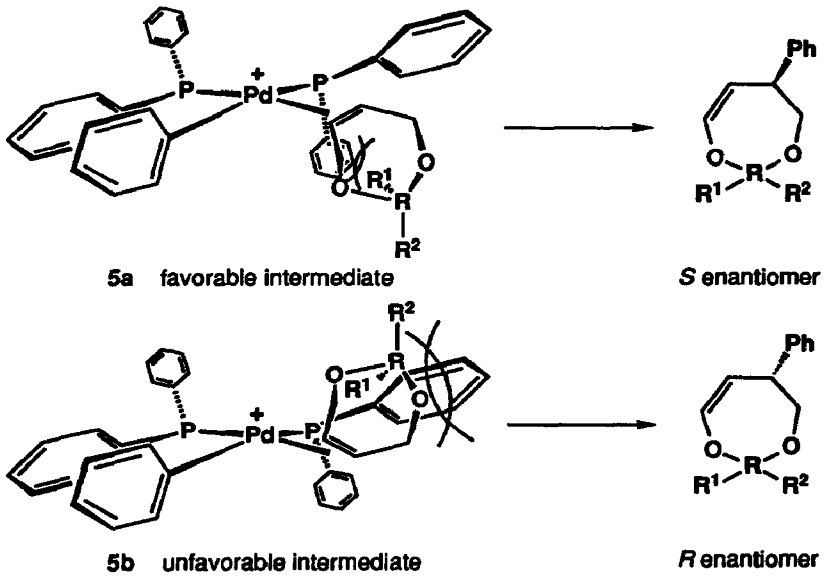


Figure 1. The binaphthyl group of (*S*)-BINAP ligand is omitted for clarity.

3 days gave the desired coupling product **2d**[11] of 72% ee in 84% yield (Table 1, entry 6).[12] The enantiomeric excess of **2d** was determined by HPLC analysis (DAICEL CHIRALCEL OD, hexane-2-propanol, 50:1), and its absolute configuration was determined by conversion of **2d** to the known lactone **4**[13] (i. *p*-TsOH in 2-butanone-H_2O (3:1), 65 °C, 13 hr, 87%, ii. Ag_2CO_3 on celite (4 equiv) in toluene, 80 °C, 10 min, 91%). Inspection of the possible modes for the olefin coordination to the $[PhPd\{(S)\text{-BINAP}\}]^+$ species[3d] indicated that steric repulsion between the substituent at C-2 and the phenyl moiety existed even in the more favorable intermediate **5a** (Figure 1), making it easy to understand why **1d** is a more appropriate substrate than **1a-c** for the asymmetric Heck reaction.

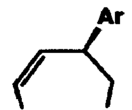
This is the first example of an effect of molecular sieves on the asymmetric Heck reaction,[14] and in an effort to better understand the role of molecular sieves in this reaction, a more detailed study was done. The results are summarized in Table 2, and clearly indicate that the composition and structure of the zeolite are important for the attainment of high enantiomeric excess and chemical yield. 3A molecular sieves gave higher yields than 4A or 5A sieves (Table 2, entries 2-4), and the use of $NaHCO_3$ or $CaCO_3$ as a base in the presence of 3A sieves gave the coupling product in low yield but nearly the same ee (entries 5-6). These results suggest that the cation of the zeolite is quite important since the best yields were observed with sieves of high K content (MS3A, K_2CO_3). Further studies are necessary to completely understand the effect of molecular sieves on the asymmetric Heck reaction.[15,16]

Table 2. Effect of Molecular Sieves on Palladium-Catalyzed Asymmetric Arylation of **1d**.[a)]

entry	base	molecular sieves	yield (%)	ee (%)
1	K_2CO_3	none	19	34
2	K_2CO_3	MS3A[b)]	82	67
3	K_2CO_3	MS4A[c)]	38	69
4	K_2CO_3	MS5A[d)]	3	73
5	$NaHCO_3$	MS3A[b)]	22	67
6	$CaCO_3$	MS3A[b)]	5	71

a) All reactionas were carried out in benzene using **1d** (4 equiv), $Pd(OAc)_2$ (3 mol %), (*S*)-BINAP (9 mol %), base (1.5 mol eq), and powdered molecular sieves at 65 °C for 3 days. b) 3A sieves = $K_9Na_3[(AlO_2)_{12}(SiO_2)_{12}]\cdot 27H_2O$. c) 4A sieves = $Na_{12}[(AlO_2)_{12}(SiO_2)_{12}]\cdot 12H_2O$. d) 5A sieves = $Ca_{4.5}Na_3[(AlO_2)_{12}(SiO_2)_{12}]\cdot 30H_2O$.

Having optimized the conditions for the formation of **2d**, we briefly explored the effect of triflate structure on the reaction. We were pleased to find that the use of other triflates under the similar reaction conditions gave the coupling products of enantiomeric excesses ranging from 60 to 75 % ee. These include the preparation of **2e** (75% ee,[17] 81% yield), **2f** (70% ee,[18] 86% yield), **2g** (67% ee,[18] 48% yield[19]), and **2h** (60% ee,[18] 73% yield).[20]



2e : Ar=*p*-Cl-Ph
2f : Ar=*p*-Me-Ph
2g: Ar=*p*-MeO-Ph
2h: Ar=2-naphthyl

Figure 2

In conclusion, we have shown that the asymmetric Heck reaction is useful for the syntheses of chiral building blocks **2d-h** and **4** in up to 75% ee. Furthermore, we have found that 3A molecular sieves can play a key role in the asymmetric Heck reaction, improving the enantiomeric excess as well as the chemical yields. Further studies are under investigation.

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4. Recently Takano *et al.* reported the palladium-catalyzed arylation of 4,7-dihydro-1,3-dioxepins and conversion of the resulting racemic 5-aryl-4,5-dihydro-1,3-dioxepins to natural products. See: a) Takano, S.; Samizu, K.; Ogasawara, K. *Synlett* 1993, 393. b) Takano, S.; Samizu, K.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* 1993, 1032.
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7. Reaction in benzene gave better results than in THF, DMSO, or DMF.
8. Under the reaction conditions, lactol **3** slowly decomposed.
9. Herbert, F. *Synthesis* 1989, 721.
10. Powdered molecular sieves purchased from Fluka.
11. spectral data of **2d**: $[\alpha]_D^{24}$ -26.5° (c 0.72, $CHCl_3$, 72% ee); IR (neat) 2869, 1469, 1174 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.36-7.20 (m, 5 H), 6.47 (dd, $J = 2.3, 7.6$ Hz, 1 H), 5.19 (d, $J = 6.9$ Hz, 1 H), 4.94 (ddd, $J = 1.0, 3.6, 7.6$ Hz, 1 H), 4.86 (d, $J = 6.9$ Hz, 1 H), 3.98 (ddd, $J = 1.0, 4.6, 11.6$ Hz, 1 H), 3.85-3.75 (m, 1 H), 3.46 (dd, $J = 8.6, 11.6$ Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 146.1, 140.9, 128.6, 127.9, 127.0, 112.0, 98.2, 76.8, 48.4; MS *m/z* 176 (M^+), 145, 117, 115 (bp); HRMS (EI) calcd for $C_{11}H_{12}O_2$ 176.0837, found 176.0849.
12. The effects of various ligands on the arylation of **1d** were as follows (benzene, no molecular sieves, $Pd(OAc)_2$ and K_2CO_3): (*S*)-BINAP (19%, 34% ee), (*S,S*)-BCPM (1%, 27% ee), (*S*)-(*R*)-BPPFA (2%, 13% ee), (*S,S*)-MOD-DIOP (7%, 21% ee). The effects of various solvents on the arylation of **1d** were as follows (no molecular sieves, $Pd(OAc)_2$, (*S*)-BINAP, and K_2CO_3): THF (12%, 11% ee), $ClCH_2CH_2Cl$ (54%, 23% ee), DMSO (14%, 10% ee), toluene (17%, 29% ee), DMF (4%, 15% ee). $ClCH_2CH_2Cl$ gave moderate results, but in the presence of molecular sieves, $ClCH_2CH_2Cl$ afforded **2d** only in 41% (20% ee).
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14. A beneficial effect of molecular sieves on asymmetric reactions using titanium or aluminum catalysts has been reported. It is thought that the water- and alcohol-scavenging properties of the sieves play an important role. See: a) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* 1987, *109*, 5765. b) Narasaka, K.; Iwasawa, N.; Inoue, M.; Yamada, T.; Nakashima, M.; Sugimori, J. *J. Am. Chem. Soc.* 1989, *111*, 5340. c) Narasaka, K.; Hayashi, Y.; Shimadzu, H.; Niihata, S. *J. Am. Chem. Soc.* 1992, *114*, 8869. d) Mikami, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc.* 1990, *112*, 3949. e) Maruoka, K.; Hoshino, Y.; Shirasaka, T.; Yamamoto, H. *Tetrahedron Lett.* 1988, *29*, 3967. Recently an interesting effect of molecular sieves on the palladium-catalyzed oxidative cyclization of dienes and copper-catalyzed aziridination of olefins has been reported. See: f) Tottie, L.; Baeckström, P.; Moberg, C. *J. Org. Chem.* 1992, *57*, 6579. g) Evans, D. A.; Faul, M. M.; Bilodeau, M. T.; Anderson, B. A.; Barnes, D. M. *J. Am. Chem. Soc.* 1993, *115*, 5328.
15. Molecular sieves were used as received. No better results were obtained when dried molecular sieves were used, suggesting that the water-scavenging effect of sieves is not important here. Powdered molecular sieves purchased from Aldrich or Wako gave comparable results.
16. Recently, we reported that silver-exchanged zeolite accelerated the asymmetric Heck reaction of alkenyl iodides. See ref. 2h and 2j.
17. Determined by HPLC analysis (DAICEL CHIRALCEL OB, hexane-2-propanol, 50:1).
18. Determined by HPLC analysis (DAICEL CHIRALCEL OD, hexane-2-propanol, 50:1).
19. 38% of *p*-methoxyphenyl triflate was recovered.
20. A representative experimental procedure is as follows (Table 1, entry 6). After degassing, a mixture of $Pd(OAc)_2$ (3.5 mg, 0.016 mmol), (*S*)-BINAP (29.2 mg, 0.047 mmol), K_2CO_3 (108 mg, 0.78 mmol), and MS3A (1 g) in benzene (1 ml) was stirred at 60 °C for 10 hr. Phenyl triflate (117.5 mg, 0.519 mmol) was added then to the red solution, and the resulting mixture was stirred at 60 °C for 20 min becoming pale purple. Addition of **1d** (210 mg, 2.1 mmol) followed, and the mixture was stirred at 60 °C until the reaction was complete (60 hr). The mixture was filtered through a layer of Florisil to remove the solid material, and after removal of solvent, the residue was purified by column chromatography (silica gel, hexane-benzene, 1:1) to give **2d** (77.3 mg, 84%) as a colorless oil.

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